



Magnitude of Diurnal Change in Retinal Vessel Density: Comparison Between Exfoliative Glaucoma and Primary Open-Angle Glaucoma

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Abstract

Objectives: The aim of this study was to investigate the magnitude of diurnal fluctuation in the superficial parafoveal vessel density (pfVD) and radial peripapillary capillary-peripapillary vessel density (RPC-ppVD) in exfoliative glaucoma (XFG) patients using optical coherence tomography angiography (OCTA) and to compare the findings with those of primary open-angle glaucoma (POAG) patients with glaucomatous damage of comparable severity.

Methods: A total of 50 patients with XFG and 48 with POAG were examined in this retrospective cross-sectional study. The OCTA readings and intraocular pressure (IOP) values were obtained at 9 am, 11 am, 2 pm, and 4 pm on the same day. The maximal change in the IOP and vessel density (VD) values was evaluated to determine the magnitude of diurnal variation.

Results: No significant difference was found in the magnitude of the average diurnal superficial-pfVD, RPC-ppVD and IOP change between the XFG and POAG groups. Comparison of the diurnal variation of sub-sector VD revealed that the magnitude of the diurnal variation in the VD of the inferonasal peripapillary and superior parafoveal regions was greater in the XFG group than that of the POAG group ($p=0.004$ and $p=0.021$, respectively). Furthermore, the differences persisted after correcting for the confounding factors of IOP, mean deviation (MD), and global retinal nerve fiber layer (RNFL) values. The magnitude of the average superficial-pfVD and the average RPC-ppVD was not correlated with the MD, total ganglion cell complex, global RNFL, or the magnitude of IOP values in either group.

Conclusion: The eyes of XFG patients demonstrated more significant diurnal fluctuation in VD (including the superior superficial-pfVD as well as the inferonasal RPC-ppVD) when compared with POAG patients, despite no statistical significance between groups in the IOP variation.

Keywords: Ganglion cell complex, magnitude of diurnal variation, optical coherence tomography angiography, parafoveal vessel density, peripapillary vessel density, retinal nerve fiber layer

Introduction

Specific optical coherence tomography angiography (OCTA) studies have already shown the extent of the fluctuations occurring in diurnal retinal vessel density (VD) in patients with

various types of glaucoma (1-9). Several studies have indicated a substantial change in retinal VD; some have demonstrated a continuing decline in retinal VD throughout the day (2,4). However, other researchers have observed that retinal VD levels were consistent the entire day (3,5,9).

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The objective of this research was to use OCTA to investigate the magnitude of diurnal fluctuation in the peripapillary (pp) and parafoveal (pf) VD in exfoliative glaucoma (XFG) patients and to compare the findings with those of primary open-angle glaucoma (POAG) patients with glaucomatous damage of comparable severity. A secondary aim was to determine if the magnitude of diurnal VD was correlated with intraocular pressure (IOP) variation, mean deviation (MD) values, or the thickness of the ganglion cell complex (GCC) and the retinal nerve fiber layer (RNFL).

Methods

This retrospective cross-sectional study included 98 individuals with glaucoma: 50 patients with XFG and 48 patients with POAG. The study participants were selected between July 2019 and February 2020. The study was conducted in compliance with the Helsinki Declaration and was approved by the Dicle University Medical Faculty Ethics Committee for Noninterventional Studies on March 5, 2020 (no: 95). All of the study participants provided written, informed consent.

The inclusion criteria required that participants were >40 years of age, had open-angle status as assessed by gonioscopic evaluation, current use of topical antiglaucoma therapy (monotherapy or combination), a best-corrected visual acuity (BCVA) of $\geq 20/40$, <1.0 diopter (D) cylindrical error and <+3.0 or >-3.0 D spherical error. Patients with a history of eye surgery were excluded; however, patients with uncomplicated cataract surgery and those with no substantial posterior capsule opacification, non-glaucomatous optic neuropathy, or a history of retinal pathology were included. The study excluded patients who were taking oral doses of carbonic anhydrase inhibitors, and those with dementia or Alzheimer's disease, a history of stroke, and those with diabetes or chronic hypertension.

The parameters used in the analysis were obtained from hospital files. The ophthalmic examination performed for all of the participants included refraction evaluation using an autorefractor (KR-890; Topcon Corp., Tokyo, Japan); BCVA and IOP measurement with a Goldmann applanation tonometer (GAT); gonioscopy and axial length (AL) assessment using an optical biometer (AL Scan; Nidek Co. Ltd., Tokyo, Japan); central corneal thickness (CCT) measurement with a Scheimpflug camera (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany); visual field parameter evaluation with regular automatic perimetry, the Swedish interactive threshold algorithm-Fast (Size 3, white stimulus), and the standard system 30-2 (Humphrey Visual Field Analyzer II, model 750; Carl Zeiss Meditec AG, Jena, Germany); OCTA parameter measurement (RTVue XR Avanti, Optovue Inc., Fremont, CA, USA); and spectral domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering

Inc., Heidelberg, Germany).

OCTA Measurements

OCTA imaging was conducted using software provided by the device manufacturer (version 2016.2.0.35). Repeated scans were used to generate 3-dimensional en face OCTA images: the first scan had dimensions of 4.5x4.5 mm and was centered over the optic nerve head (ONH) using the Angio Disc mode. The second scan had proportions of 6x6 mm and was located over the fovea using the Angio Retina mode. A VD calculation was generated automatically using the blood vessel area data. The following step involved obtaining and reviewing VD values (expressed as %) of the macula's superficial parafoveal retinal OCTA scans and the radial peripapillary network of the ONH (RPC; ONH's superficial capillary plexus). An annulus with an external and internal diameters of 3 mm and 1 mm, respectively, encompassed the parafoveal VD to be computed. The RPC layer consists of the area between the internal limiting membrane and the RNFL outer boundary. The elliptical annulus, with a width of 0.75 mm and originating from the optic disc boundary, constituted the peripapillary area. GCC thickness was measured using macula scanning. The resulting map provided the average thickness of the total GCC in micrometers (μm).

OCT Measurements

OCT scans to evaluate the peripapillary RNFL imaging centered on a 3.45-mm circle in the center of the optic disc. The thickness of the peripapillary global RNFL was calculated in μm , and the data collected were analyzed. A single trained examiner evaluated the OCT images. The complete absence of movement artifacts and proper centering of the scans was confirmed, and images with a quality score of <20 and those with inaccuracies in segmentation, centering, or illumination were excluded.

Diurnal Measurements

IOP evaluation and OCTA imagery were performed using GAT at 4 intervals in a single day: 9 am, 11 am, 2 pm, and 4 pm. All of the OCTA measurements were performed under fixed conditions at a single site with stable air-conditioning provisions and a darkened environment. A single technician conducted all of the OCTA measurements. A professional independent grader, whose identity was concealed from the study participants, analyzed the OCTA images. Images with a signal strength of ≥ 58 and no segmentation loss were included in the analysis.

The mean values were presented as the average of the 4 time-point measurements, and the degree of diurnal variability was calculated based on the maximum difference calculated in the IOP and VD values. That is, the difference obtained when the minimum numerical measurement is subtracted from the maximum value.

Statistical Analysis

SPSS for Windows, Version 15.0 (SPSS Inc., Chicago, IL, USA) and an InStat demo version (GraphPad Software Inc., San Diego, CA, USA) were used to conduct the statistical analysis. The test-retest variance was measured using intra-class correlation coefficients (ICCs). The ICC evaluation was completed based on a combination of 4 measurements taken by the same person at the same location (10). The mean±SD was used to describe continuous variables, while the count (frequency) was used for categorical variables. A chi-squared test and the Fisher exact test were used to compare classes of categorical variables. Two groups were compared using the Mann-Whitney U test. One-way analysis of covariance (ANCOVA) was also performed after adjusting for IOP, MD, and global RNFL values to evaluate the association between the retinal VD of the XFG and POAG groups. The Friedman test was performed to evaluate diurnal differences in the groups. The Pearson correlation coefficient was used to evaluate the relationship between 2 continuous variables in the groups. The findings were considered significant at a 95% confidence interval with an agreed p value of <0.05.

Results

In total, 98 eyes were examined: 50 eyes of XFG patients and 48 eyes of POAG patients. The XFG and POAG groupings were not significantly different in the distribution of gender, age, CCT, laterality, AL, IOP, BCVA, lens status, total GCC, global RNFL, MD, signal strength index (SSI), duration of glaucoma, duration of therapy, or number of antiglaucoma molecules used ($p>0.05$; Table 1). Table 2 shows a comparison of groups according to antiglaucoma drug use. No substantial variations in use of antiglaucoma drug were observed between groups, with the exception of the rate of usage of a prostaglandin analogue (chi-squared test, $p<0.001$; Table 2). Table 3 illustrates the ICC values recorded for all of the measurement areas in all of the participants from both the XFG and POAG groups. The ICC ranged from 0.757 to 0.985 in the XFG patients and from 0.834 to 0.985 in the POAG patients. Repeatability in the parafoveal and peripapillary areas was confirmed in both groups.

The parafoveal VD of the superficial macular layer (nasal, temporal, inferior, superior, and average), as well as the peripapillary area of the radial peripapillary region (temporal,

Table 1. Demographic and clinical characteristics of patients with XFG and POAG

	XFG group (n=50)	POAG group (n=48)	p
Age (years)	56.46±6.91	55.46±13.10	0.980*
Sex (female/male)	11/25 (31/69)	13/21 (38/62)	0.420†
Laterality (right/left)	27/23 (54/46)	24/24 (50/50)	0.786†
BCVA	0.77±0.23	0.83±0.18	0.246*
CCT (μm)	512.48±37.89	510.92±17.60	0.723*
AL (mm)	23.70±0.92	23.36±0.90	0.061*
Lens status (phakic/pseudophakic)	42/8 (84/16)	40/8 (83/17)	>0.999§
IOP baseline (mmHg)	30.88±6.63	30.13±6.16	0.745*
IOP treated (mmHg)	15.80±2.51	17.01±1.91	0.058*
Glaucoma duration (year)	3.26±1.21	3.69±1.95	0.222*
Therapy duration (year)	2.73±1.19	3.32±1.87	0.129*
Number of molecules (n)	2.70±0.86	2.92±0.87	0.169*
Global RNFL thickness (μm)	82.88±21.09	66.67±21.63	0.124*
Total GCC thickness (μm)	88.03±17.81	80.38±17.99	0.222*
MD (dB)	-8.38±7.02	-8.41±7.81	0.578*
SSI superficial-pfVD	75.31±9.08	77.10±5.93	0.741*
SSI RPC-ppVD	75.39±9.91	76.05±6.66	0.818*

Data are shown as the mean±SD or n (%); Bold values are significant ($p<0.05$); *: Mann-Whitney U test; †: Chi-squared test; §: Fisher exact test; AL: Axial length; BCVA: Best corrected visual acuity; CCT: Central corneal thickness; GCC: Ganglion cell complex; IOP: Intraocular pressure; MD: Mean deviation; pfVD: Parafoveal vessel density; POAG: Primary open-angle glaucoma; ppVD: Peripapillary vessel density; RNFL: Retinal nerve fiber layer; RPC: Radial peripapillary capillary; SSI: Signal strength index; XFG: Exfoliative glaucoma.

Table 2. Comparison of antiglaucoma drug use between XFG and POAG subjects

	XFG group (n=50)	POAG group (n=48)	p
Beta-blocker+Carbonic anhydrase inhibitor			
No	14 (28.0)	24 (50.0)	0.053*
Yes	36 (72.0)	24 (50.0)	
Beta-blocker+Prostaglandin analogue			
No	42 (84.0)	40 (83.0)	1.00*
Yes	8 (16.0)	8 (17.0)	
Alpha-2 adrenergic agonist			
No	23 (46.0)	16 (33.0)	0.283*
Yes	27 (54.0)	32 (67.0)	
Prostaglandin analogue			
No	35 (70.0)	14 (29.0)	<0.001*
Yes	15 (30.0)	34 (71.0)	
Beta-blocker+Alpha-2 adrenergic agonist			
No	48 (96.0)	44 (92.0)	0.431**
Yes	2 (4.0)	4 (8.0)	
Carbonic anhydrase inhibitor			
No	46 (92.0)	44 (92.0)	1.00**
Yes	4 (8.0)	4 (8.0)	

Bold values are significant ($p < 0.05$); *, Chi-squared test; **, Fisher exact test; POAG: Primary open-angle glaucoma; XFG: Exfoliative glaucoma.

Table 3. Intraclass correlation coefficient for each measurement region in XFG and POAG groups

	XFG group (n=50)			POAG group (n=48)		
	ICC	p	95% CI	ICC	p	95% CI
Superficial-pfVD (%)						
Average	0.893	<0.0001	0.805-0.947	0.933	<0.0001	0.876-0.968
Temporal	0.815	<0.0001	0.665-0.908	0.896	<0.0001	0.806-0.950
Superior	0.826	<0.0001	0.683-0.914	0.948	<0.0001	0.904-0.975
Nasal	0.884	<0.0001	0.789-0.943	0.860	<0.0001	0.741-0.933
Inferior	0.860	<0.0001	0.746-0.931	0.913	<0.0001	0.839-0.958
RPC-ppVD (%)						
Average	0.960	<0.0001	0.927-0.980	0.972	<0.0001	0.949-0.987
Nasal	0.960	<0.0001	0.928-0.980	0.985	<0.0001	0.973-0.993
Inferonasal	0.887	<0.0001	0.795-0.944	0.971	<0.0001	0.945-0.986
Inferotemporal	0.908	<0.0001	0.832-0.954	0.980	<0.0001	0.963-0.991
Superotemporal	0.969	<0.0001	0.943-0.984	0.972	<0.0001	0.947-0.986
Superonasal	0.888	<0.0001	0.797-0.944	0.974	<0.0001	0.951-0.988
Temporal	0.906	<0.0001	0.830-0.954	0.945	<0.0001	0.897-0.973

Bold values are significant ($p < 0.05$); CI: Confidence interval; ICC: Intraclass correlation coefficient; pfVD: Parafoveal vessel density; POAG: Primary open-angle glaucoma; ppVD: Peripapillary vessel density; RPC: Radial peripapillary capillary; XFG: Exfoliative glaucoma.

superonasal, superotemporal, inferotemporal, inferonasal, nasal, and average) was studied in detail. No statistically relevant diurnal variation in the IOP and VD values was identified in any parafoveal or peripapillary area in intra-group measurements (Friedman test, $p>0.05$). Figure 1 shows the curves of diurnal variation for the average superficial-pfVD and average RPC-ppVD values of both the XFG and POAG patients.

Magnitude of Diurnal Variation of Superficial-pfVD, RPC-ppVD, and IOP Measurements

Differences in the diurnal parafoveal and peripapillary VD and IOP between the XFG and POAG groups are presented in Table 4. No considerable difference between groups was seen in the magnitude of the average superficial-pfVD, average RPC-ppVD, or the IOP ($p>0.05$; Table 4). Contrasting the diurnal variation value in the sub-sector peripapillary area with the VD value of the sub-sector parafoveal area revealed that the amplitude of diurnal variations of the inferonasal peripapillary as well as the superior parafoveal VD values of the XFG patients were higher than those of the POAG patients ($p=0.004$ and $p=0.021$; Table 4). Furthermore, when the mean IOP-, MD-, and global RNFL-adjusted relationships of the superficial-pfVD and RPC-ppVD of the XFG and POAG groups were examined with one-way ANCOVA, significant inter-group differences were remained (for inferonasal RPC-ppVD and superior superficial-pfVD, $p<0.001$).

In the XFG group, the magnitude of diurnal change in the average superficial-pfVD was lower in eyes treated with a beta (β)-blocker+carbonic anhydrase inhibitor combination drug (Mann-Whitney U test, not using [n:14]: $6.98\pm2.31\%$ and using [n:36]: $5.56\pm2.93\%$; $p=0.039$), and the magnitude of diurnal change in the average RPC-ppVD was higher in eyes treated with a prostaglandin analogue (Mann-Whitney U test, not using [n:35]: $4.57\pm3.19\%$ and using [n:15]: $7.92\pm3.85\%$; $p=0.002$). In the POAG group, the magnitude of diurnal change in the average superficial-pfVD was lower in eyes treated with a β -blocker+ α -2 adrenergic agonist combination (Mann-Whitney U test, not using [n:44]: $4.3\pm2.47\%$ and using [n:4]: $2.16\pm1.02\%$; $p=0.038$), a β -blocker+carbonic anhydrase inhibitor combination (Mann-Whitney U test, not using [n:24]: $4.98\pm2.58\%$ and using [n:24]: $3.26\pm2.01\%$; $p=0.049$), and a prostaglandin analogue (Mann-Whitney U test, not using [n:14]: $4.89\pm1.14\%$ and using [n:34]: $3.81\pm2.77\%$; $p=0.017$). There was no statistically significant difference in the magnitude of diurnal change in retinal VD between the 2 groups in terms of other drug use.

The mean and magnitude values of the clinical factors affecting retinal VD in the 2 groups are provided in Tables 5 and 6. In the XFG eyes, the total GCC and global RNFL

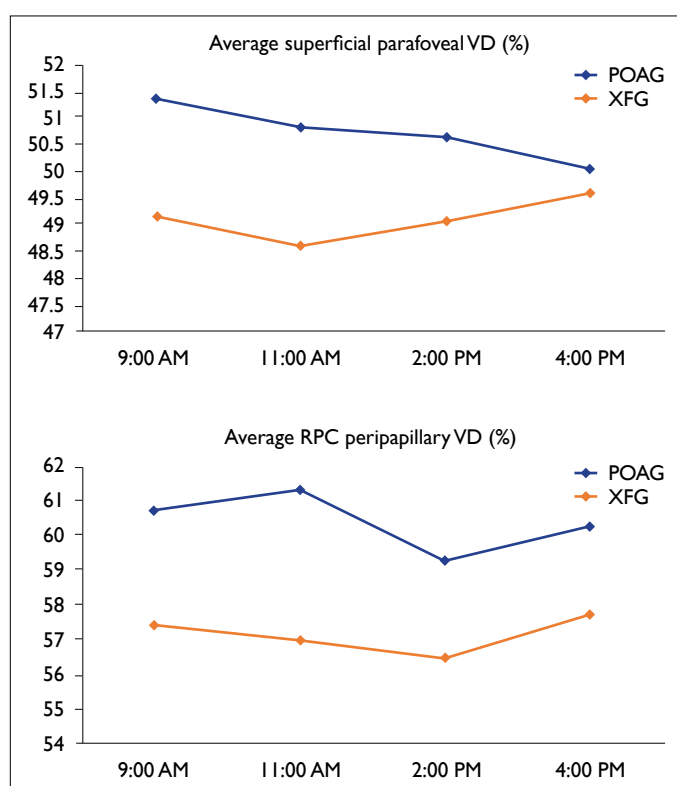


Figure 1. Graph of the patterns of diurnal variation of average superficial-parafoveal (pf) vessel density (VD) and average radial peripapillary capillary-peripapillary vessel density (RPC-ppVD) in exfoliative glaucoma (XFG) and primary open-angle glaucoma (POAG) patients. VD values were recorded between 9:00 am and 4:00 pm. The VD variations in each group were analyzed with the Friedman test (Average superficial-pfVD: XFG: $p=0.606$, POAG: $p=0.310$; average RPC-ppVD: XFG: $p=0.696$; POAG: $p=0.333$).

thickness had a direct proportionate effect on the mean average RPC-ppVD. In the POAG eyes, the mean average RPC-ppVD was significantly positively correlated with the MD, global RNFL thickness, and the total GCC thickness. In the macular area, the mean average superficial-pfVD was associated with the MD and the global RNFL thickness in the POAG group. It was also observed in the POAG group that longer glaucoma and therapy duration was associated with lower retinal VD values (Table 5).

The XFG group and the POAG group findings did not demonstrate any association between the MD, total GCC, global RNFL, or the scale of IOP and the magnitude of the average superficial-pfVD or the average RPC-ppVD (Table 6). In the POAG group, the duration of glaucoma and therapy proportionally affected the magnitude of diurnal change in the average superficial-pfVD. In both the XFG and the POAG groups, the magnitude of diurnal change in the average superficial-pfVD was significantly negatively correlated with the number of antiglaucoma molecules used (Table 6).

Table 4. Magnitude of diurnal variation of retinal vessel density and IOP values of XFG and POAG subjects

	XFG group (n=50)	POAG group (n=48)	*p
Δ superficial-pfVD (%)			
Average	5.99 $\pm$ 2.80	4.12 $\pm$ 2.47	0.076
Temporal	7.01 $\pm$ 4.91	4.97 $\pm$ 3.05	0.216
Superior	8.00 $\pm$ 3.87	4.75 $\pm$ 2.35	0.021
Nasal	6.66 $\pm$ 3.30	5.02 $\pm$ 3.64	0.133
Inferior	7.73 $\pm$ 4.17	5.65 $\pm$ 3.04	0.436
Δ RPC-ppVD (%)			
Average	5.70 $\pm$ 3.72	4.90 $\pm$ 3.74	>0.999
Nasal	6.37 $\pm$ 3.48	4.88 $\pm$ 2.41	0.560
Inferonasal	11.55 $\pm$ 8.67	5.28 $\pm$ 3.60	0.004
Inferotemporal	9.93 $\pm$ 7.61	6.27 $\pm$ 3.66	0.226
Superotemporal	7.25 $\pm$ 3.89	7.36 $\pm$ 5.86	>0.999
Superonasal	10.29 $\pm$ 9.42	5.79 $\pm$ 3.85	0.068
Temporal	9.20 $\pm$ 5.31	7.25 $\pm$ 4.45	0.577
Δ IOP (mmHg)	3.35 $\pm$ 1.87	4.12 $\pm$ 2.59	>0.999

Data are shown as the mean $\pm$ SD; Bold values are significant ($p<0.05$); *: Mann-Whitney U test, XFG vs. POAG groups; Δ : Change in values (mathematical subtraction of minimum value from maximum value); IOP: Intraocular pressure; pfVD: Parafoveal vessel density; POAG: Primary open-angle glaucoma; ppVD: Peripapillary vessel density; RPC: Radial peripapillary capillary; XFG: Exfoliative glaucoma.

Table 5. Correlation between mean retinal vessel density and glaucoma duration, therapy duration, number of molecules used, global RNFL thickness, total GCC thickness, MD, and IOP values in XFG and POAG patients

	XFG group (n=50)				POAG group (n=48)			
	Mean superficial pfVD (%)		Mean RPC ppVD (%)		Mean superficial pfVD (%)		Mean RPC ppVD (%)	
	R	P	R	P	R	P	R	P
Glaucoma duration (years)	-0.123	0.394	-0.081	0.577	-0.785	<0.001	-0.750	<0.001
Therapy duration (years)	-0.139	0.334	-0.069	0.632	-0.792	<0.001	-0.742	<0.001
Number of molecules (n)	-0.003	0.985	-0.269	0.059	0.165	0.264	-0.188	0.201
Mean IOP (mmHg)	0.038	0.853	-0.149	0.466	0.227	0.285	-0.064	0.767
Global RNFL (μ m)	0.332	0.105	0.530	0.006	0.412	0.046	0.720	-0.001
Total GCC (μ m)	0.212	0.299	0.450	0.021	0.185	0.386	0.526	0.008
MD (dB)	-0.175	0.460	-0.174	0.464	0.506	0.027	0.815	-0.001

Pearson's R (p value); Bold values are significant ($p<0.05$); GCC: Ganglion cell complex; IOP: Intraocular pressure; MD: Mean deviation; pfVD: Parafoveal vessel density; POAG: Primary open-angle glaucoma; ppVD: Peripapillary vessel density; RNFL: Retinal nerve fiber layer; RPC: Radial peripapillary capillary; XFG: Exfoliative glaucoma.

Discussion

Previous studies have examined patients with XFG and POAG to assess the OCTA-based macular (7,11) and peripapillary (5,12-14) regions individually and together (9,15-

18). Some of the results are consistent with our current research (11,12,14,17). Several of these studies recorded observations once daily (11-14,16,18), while a few used multiple observations, ranging from 2 to 5 per day. Considerable

Table 6. Correlation between magnitude of retinal vessel density fluctuation and glaucoma duration, therapy duration, number of molecules used, global RNFL thickness, total GCC thickness, MD value, and magnitude of IOP fluctuation in XFG and POAG patients

	XFG group (n=50)				POAG group (n=48)			
	Δ superficial pfVD (%)		Δ RPC ppVD (%)		Δ superficial pfVD (%)		Δ RPC ppVD (%)	
	R	P	R	P	R	P	R	P
Glaucoma duration (years)	-0.016	0.912	0.147	0.310	0.430	0.002	-0.135	0.359
Therapy duration (years)	0.011	0.938	0.169	0.242	0.451	0.001	-0.139	0.345
Number of molecules (n)	-0.304	0.032	0.116	0.422	-0.412	0.004	0.165	0.262
Δ IOP (mmHg)	0.188	0.359	-0.135	0.512	0.123	0.566	-0.010	0.962
Global RNFL (μ m)	-0.062	0.769	0.247	0.234	0.103	0.633	0.026	0.903
Total GCC (μ m)	0.012	0.954	0.252	0.214	0.061	0.775	0.026	0.905
MD (dB)	0.286	0.221	0.158	0.506	-0.162	0.506	-0.044	0.857

Pearson's R (p value); Bold values are significant ($p < 0.05$); Δ : Change in values (mathematical subtraction of minimum value from maximum value); GCC: Ganglion cell complex; IOP: Intraocular pressure; MD: Mean deviation; pfVD: Parafoveal vessel density; POAG: Primary open-angle glaucoma; ppVD: Peripapillary vessel density; RNFL: Retinal nerve fiber layer; RPC: Radial peripapillary capillary; XFG: Exfoliative glaucoma.

reduction in retinal VD in XFG eyes has been reported by some researchers (11-13), while others did not find a difference between the retinal VD assessments of XFG and POAG eyes (15).

Our study compared the diurnal VD values recorded using OCTA in both the superficial parafoveal and the peripapillary RPC regions of XFG and POAG patients. Our primary findings were that the magnitude of the average RPC-ppVD, average superficial-pfVD, and IOP variations of the XFG and POAG groups were not statistically significantly different. Analysis of the magnitude of the sub-sector retinal VD values revealed that more considerable diurnal variation occurred in the VD values of the inferonasal RPC and the superior superficial parafoveal regions in the XFG patients when compared with the POAG patients. Finally, when the relationship between the VD parameters of the XFG and POAG groups was examined after adjusting for the IOP, MD and global RNFL values, a significant difference between the groups persisted.

Recently, a study conducted by Jo et al. (15) considered 49 POAG-affected and 49 XFG-affected eyes. The age-, IOP-, AL-, SSI- and RNFL-adjusted outcomes of the research yielded a clinically insignificant difference in the peripapillary and macular VD values as determined by OCTA between the POAG and XFG patients of similar age and glaucoma severity. We did not correct the OCTA images for SSI; however, only high-quality OCTA scans (SSI ≥ 58) were included and no statistically significant SSI differences between the groups were found. No considerable variation was detected between the XFG and POAG group eyes in age, CCT, AL, BCVA, lens

status, duration of glaucoma/therapy, the number of antiglaucoma molecules used, MD, or GCC/RNFL thickness.

No significant association was seen between the levels of diurnal variation of VD and those of IOP in our research. Müller et al. (4) carried out a cross-sectional study in which they examined 40 eyes from 40 patients with POAG. Examinations (RPC, deep and superficial retinal) were completed at 4 time points (8 am, 11 am, 3 pm, and 8 pm) on 2 consecutive days. Deep retinal OCTA of the macula demonstrated considerable diurnal variation. According to this research, flow density was not significantly affected by fluctuations in the IOP. These findings are consistent with our results and those of Mansouri et al. (1), in which OCTA imaging and IOP computation were conducted on a single day at 8 am, 11 am, 2 pm, and 4 pm.

Numerous studies have noted a correlation between reduced VD and structural damage, as demonstrated by the RNFL and GCC thicknesses (12, 19-21). In the current study, although the mean retinal VD value was found to be correlated with the total GCC, global RNFL, and MD values, the magnitude of retinal VD was not correlated with the total GCC or global RNFL and MD values of either the XFG or the POAG groups. Participant use of medications, including topical antiglaucoma treatment, was not discontinued in our study. In both the XFG and the POAG eyes, the use of fewer antiglaucoma molecules was associated with a greater magnitude of diurnal change in the superficial-pfVD. Diurnal fluctuation in retinal VD values decreased when more ocular hypotensive molecules were utilized. In both groups,

the magnitude of diurnal change in the average superficial-pfVD was lower in eyes treated with a β -blocker+carbonic anhydrase inhibitor combination. However, it would not be appropriate to say that the use of a β -blocker and carbonic anhydrase inhibitor drug reduces daily fluctuation, since almost all of our patients used combination therapy and the sample size for subgroup analysis was small. Hence, the association between the real magnitude of retinal VD variation and the clinical properties and the structural and functional parameters may not be precise.

The primary limitation of this study is the failure to evaluate systemic parameters. Although the patients enrolled in the study had used antiglaucoma medication for a similar length of time, the study outcomes cannot be generalized. The study outcomes would have had better reliability and generalization potential if the diurnal fluctuation in participants had also been ascertained before drug use. The study did not include a control group since the disparity in retinal VD between the glaucomatous eyes and the healthy eyes was already known (2,5). This research was designed to compare the macular and peripapillary vasculature of XFG and POAG groups. Finally, greater accuracy might have been achieved if the study had included day and night observations of systemic parameters and evaluation of ocular mechanical and vascular parameters.

The results indicated that the eyes of the XFG patients demonstrated more significant diurnal fluctuation in VD (the superior parafoveal VD as well as the inferonasal peripapillary VD) in comparison with the POAG patients, despite no statistical significance in the amplitude of the average RPC-pVD and superficial-pfVD, as well as the IOP variations between the groups. The main drawback associated with daytime monitoring is that fluctuation in IOP and VD occurring outside of typical office hours is not recorded. This is predominantly the case with glaucoma patients who have irregular IOP patterns, like those with XFG (12,22). Hence, the most accurate IOP and VD profile can only be obtained with 24-hour IOP monitoring.

It may be that 24-hour monitoring of IOP and retinal hemodynamics is essential, particularly when it comes to high-risk patients with a larger fluctuating diurnal retinal VD and the target IOP seems to have been achieved. The clinical management of XFG patients may be altered as a result of 24-hour monitoring. The outcomes of this study provide a foundation for future research with considerations such as a longer follow-up period and a larger sample.

Disclosures

Ethics Committee Approval: The study was conducted in compliance with the Helsinki Declaration and was approved by the Dicle University Medical Faculty Ethics Committee for Noninterventional Studies on March 5, 2020 (no: 95).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (AAD, SE, MK, UK); preparation and review of the study (AAD, UK); data collection (AAD, SE, MK); and statistical analysis (AAD).

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